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The Cholesterol-5,6-Epoxyde Hydrolase: A Metabolic Checkpoint in Several Diseases

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Philippe de Medina, Silia Ayadi, Khadijetou Diallo, Julio Buñay, Laly Pucheu, Regis Soulès, Michel Record, Severine Brillouet, Lavinia Vija, Frederic Courbon, Sandrine Silvente-Poirot, and Marc Poirot

10

Abstract

11 Cholesterol-5,6-epoxides (5,6-ECs) are
12 oxysterols (OS) that have been linked to sev-
13 eral pathologies including cancers and neuro-
14 degenerative diseases. 5,6-EC can be produced
15 from cholesterol by several mechanisms
16 including reactive oxygen species,

lipoperoxidation, and cytochrome P450 17
enzymes. 5,6-EC exists as two different 18
diastereoisomers: 5,6 α -EC and 5,6 β -EC with 19
different metabolic fates. They can be pro- 20
duced as a mixture or as single products of 21
epoxidation. The epoxide ring of 5,6 α -EC 22
and 5,6 β -EC is very stable and 5,6-EC is 23
prone to hydration by the cholesterol-5,6- 24
epoxide hydrolase (ChEH) to give 25
cholestane-3 β ,5 α ,6 β -triol, which can be fur- 26
ther oxidized into oncosterone. 5,6 α -EC is 27
prone to chemical and enzymatic conjugation 28
reaction leading to bioactive compounds such 29
as dendrogenins highlighting the existence of a 30
new metabolic branch on the cholesterol path- 31
way centered on 5,6 α -EC. We will summarize 32
in this chapter current knowledge on this path- 33
way which is controlled by the ChEH. 34

Philippe de Medina, Sandrine Silvente-Poirot and Marc Poirot contributed equally with all other contributors.

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Keywords

Cholesterol · Sterols · Oxysterol ·
Oncosterone · Dendrogenins · Cancer · Cell
differentiation · Autophagy · Exosomes

8.1 Introduction

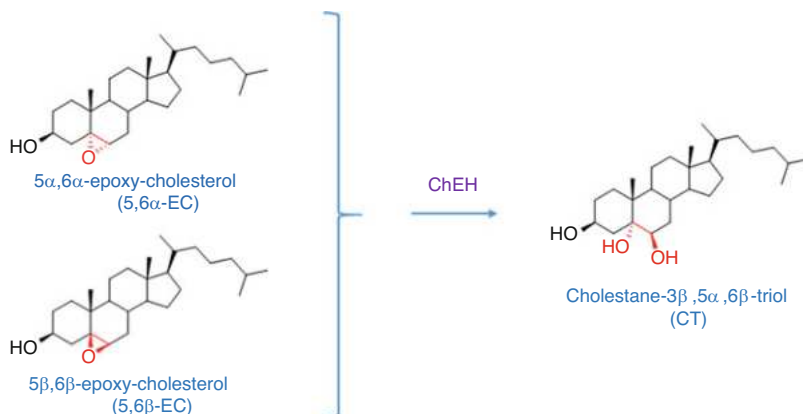
The epoxide hydrolases (EHs) constitute a family of enzymes present in all organisms, which transform epoxide containing lipids by the addition of water to give a *trans*-diol. An epoxide (or oxirane) is a three-membered cyclic ether. Five EHs have been described in vertebrates which are: soluble EH (sEH), microsomal EH (mEH), cholesterol EH (Cholesterol-5,6-epoxide hydrolase or ChEH), hepoxilin hydrolase, and leukotriene A4 (LTA4) hydrolase (Morisseau 2013; Newman et al. 2005). ChEH (EC 3.3.2.11) represents a distinct subset among EHs with respect to its substrate specificity, activity, and molecular identity. ChEH is very selective for the cholesterol-5,6-epoxide (5,6-EC) diastereoisomers: cholesterol-5 α ,6 α -epoxide (5,6 α -EC) and cholesterol-5 β ,6 β -epoxide (5,6 β -EC) and catalyzes their stereoselective hydration into cholestane-3 β ,5 α ,6 β -triol (CT) (Silvente-Poirot and Poirot 2012; Sevanian and Mcleod 1986; Nashed et al. 1985) (Fig. 8.1). ChEH has stimulated the interest of researchers when 5,6-EC was suspected of being involved in skin carcinogenesis (Chan and Black 1974; Lo and Black 1973; Black and Lo 1971). Because of

the presence of the epoxide group, it was supposed that 5,6-EC could react spontaneously with nucleophiles and behave like alkylating agents with direct carcinogenic properties. However, contradictory results were published concerning the potential carcinogenic and mutagenic effects of 5,6-ECs. This was reviewed in (Poirot and Silvente-Poirot 2013). In addition, the potential alkylating activity of 5,6-EC was recently ruled out by showing that 5,6-EC is stable and un-reactive toward nucleophiles under non-catalytic conditions (Paillasse et al. 2012). The present review is focused on ChEH and its relationship with cholesterol biosynthesis in connection with cancer and neurodegenerative diseases.

8.2 The ChEH Enzyme

ChEH was characterized at the molecular level as being a pharmacological target of tamoxifen, a drug widely used and approved by the FDA for the treatment and the prevention of breast cancers (BC) expressing the estrogen receptor alpha (ESR1). The ChEH is a hetero-oligomeric proteinaceous complex made mainly of two different enzymes involved on the post-lanosterol cholesterol biosynthesis: (1) the 3 β -hydroxysteroid- Δ 8, Δ 7-isomerase also named as the emopamil-binding protein (EBP) or delta8-delta7-isomerase (D8D7I), which catalyzes the isomerization of zymosterol (5 α -cholest-8-en-3 β -ol) and zymosterol (5 α -cholestadien-8,24-en-3 β -ol) into

Fig. 8.1 The cholesterol-5,6-epoxide hydrolase (ChEH) catalyzes the trans hydration of 5,6 α - and 5,6 β -epoxycholesterol to give cholestane-3 β ,5 α ,6 β -triol



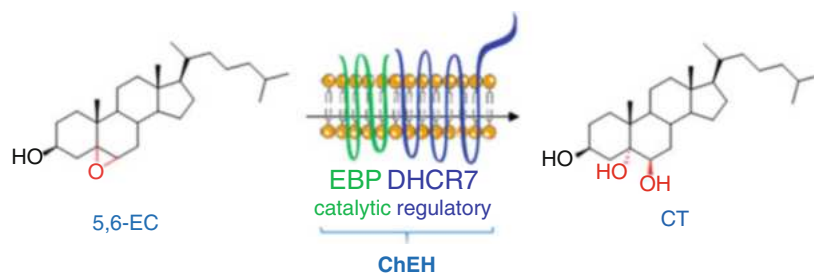


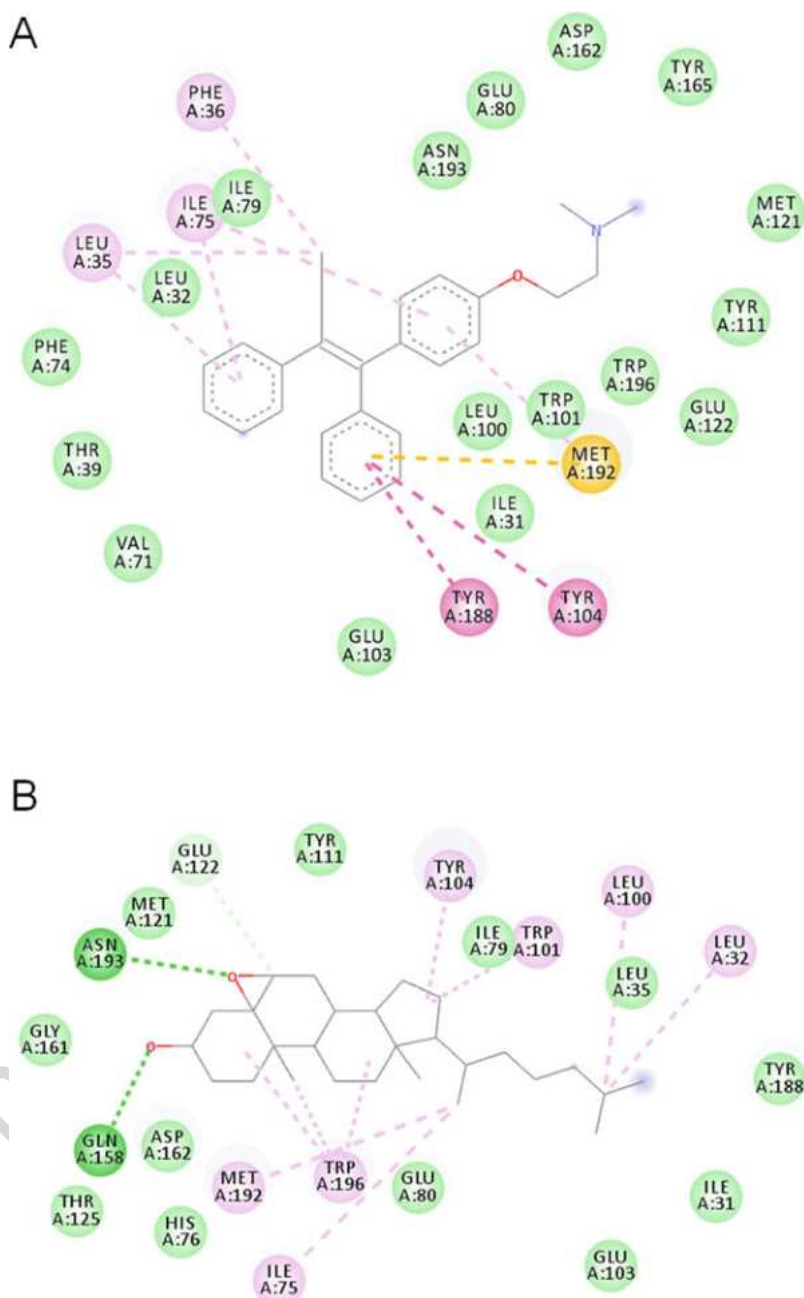
Fig. 8.2 The ChEH is heterodimer of EBP and DHCR7. EBP is the catalytic subunit and DHCR7 is the regulatory subunit

lathosterol (5α -cholest-7-en- 3β -ol) and 24-dehydrolathosterol (5α -cholestadien-7,24-en- 3β -ol), respectively; (2) the 3β -hydroxysteroid- Δ 7-reductase (DHCR7) that converts 7-dehydrocholesterol and 7 (cholesta-5,7-dien- 3β -ol) and (cholesta-5,7,24-trien- 3β -ol) into cholesterol and desmosterol. EBP and DHCR7 were found necessary and sufficient to reconstitute the ChEH (De Medina et al. 2010; Kedjouar et al. 2004). EBP was shown to carry out the catalytic activity of the ChEH, while DHCR7 was the regulatory subunit of the ChEH (Fig. 8.2). The crystal structure of EBP was published in the presence of Tamoxifen (PDB: 6OHU) (Long et al. 2019). Tamoxifen was shown to be a competitive inhibitor of ChEH (De Medina et al. 2010), and docking experiments of EBP showed that 5,6-EC fits well within the tamoxifen binding site of EBP (Fig. 8.3). Our team reported that the ChEH was identical to the microsomal anti-estrogen binding site (AEBS), a high affinity microsomal binding site for tamoxifen and related compounds (Leignadier et al. 2017; De Medina et al. 2010; Kedjouar et al. 2004). It was found that all the tested AEBS ligands were inhibitors of the ChEH and oxysterols known as substrates or inhibitors of ChEH were found ligands of the AEBS (De Medina et al. 2010; Sevanian and Mcleod 1986). It was also found that their affinity for the AEBS correlated positively with their potency to inhibit the ChEH (De Medina et al. 2010). Other proteins such as the microsomal epoxide hydrolase (mEH) and the 3β -hydroxysteroid- Δ 24-reductase (DHCR24) were found to affect ChEH activity and the AEBS pharmacological profile when co-expressed with EBP and DHCR7 (M Poirot, unpublished results). ChEH is a promiscuous enzyme that binds drugs belonging to different pharmacological classes including selective estrogen receptors modulators such as Tamoxifen, diphenylmethane compounds such as tesmilifene, phenothiazines, and amiodarone (Silvente-Poirot and Poirot 2012). It includes also natural compounds such as B-ring oxysterols (CT, OCDO, 7-hydroxy- and 7-ketocholesterol) (Silvente-Poirot and Poirot 2012), dendrogenin A (De Medina et al. 2013), and polyunsaturated fatty acids including oleic, arachidonic, and docosahexaenoic acids (De Medina et al. 2010). Recent inhibitors of EBP such as TASIN inhibitors developed for the treatment of colorectal cancers (Theodoropoulos et al. 2020; Wang et al. 2019; Zhang et al. 2018; Zhang et al. 2016) or for the remyelination of dendrocytes (Sax et al. 2022; Caprariello and Adams 2022; Han and Zhou 2019; Hubler et al. 2018) have been reported. These compounds are likely to be ChEH inhibitors and their evaluation deserves further investigations.

8.3 5,6-EC Formation and Stability

The ChEH activity requires 5,6-EC for producing its hydration product CT. Conditions that were listed to be required for 5,6-EC production have been reviewed before (Poirot and Silvente-Poirot 2013) (Fig. 8.4). These include some reactive oxygen species, lipoperoxidation, and cytochrome p450 for the stereoselective production of $5,6\alpha$ -EC. The existence of a cytochrome p450

Fig. 8.3 Molecular modeling of the putative catalytic site of the ChEH after docking of 5,6 β -EC into the EBP. (a) Two-dimensional topography of the tamoxifen binding site on EBP (obtained using Discovery Studio v 2021). (b) Two-dimensional topography of the 5,6 β -EC binding site on EBP highlighting that ASN193 could act as a proton donor as catalyst of the 5,6-epoxide ring opening. *Interactions:* very light green: carbon Hydrogen bond; light green: van der Waals; dark green: conventional Hydrogen bond; orange: pi-sulfur; dark pink: pi-pi T-shaped; light pink: alkyl, pi-alkyl



involved in the stereoselective production of 5,6 α -EC (Watabe and Sawahata 1979) supports the existence of specific metabolic branch based on 5,6 α -EC transformation. Interestingly, recent studies from Zielinski et al showed that cholesterol epoxidation with a peroxide can give variable ratios of both diastereoisomers depending on the presence of a proton donor at proximity of the

reaction (Zielinski and Pratt 2019). This suggests that even lipoperoxidation could give one or the other isomer as a main product according to the biochemical context in which the reaction takes place.

It was postulated that 5,6-EC could be potent alkylating substances, like other chemicals bearing epoxide groups such as styrene oxides, but

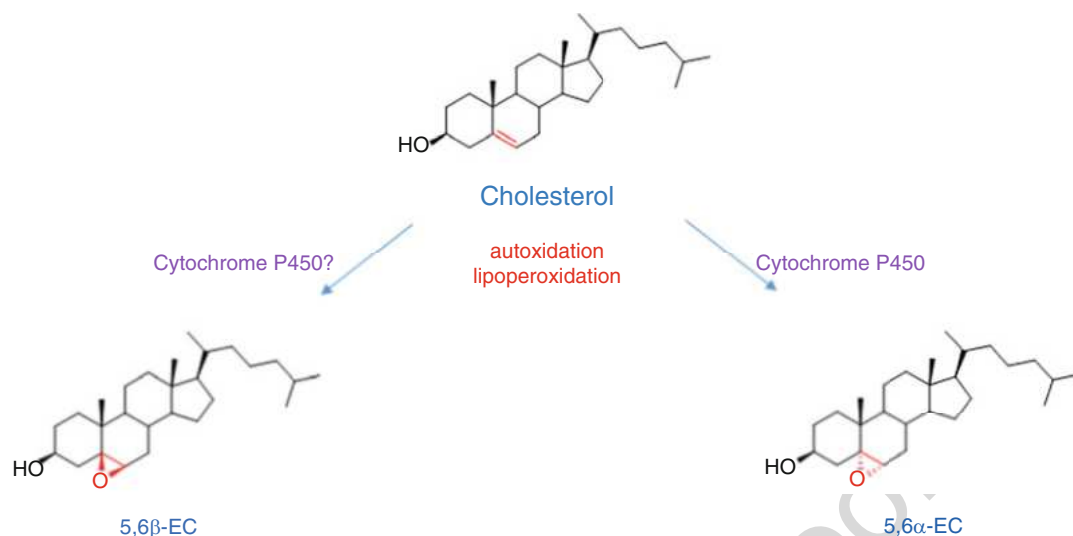


Fig. 8.4 5,6-EC formation and biosynthesis. 5,6-EC can be produced from cholesterol by different nonenzymatic and enzymatic mechanisms

181 5,6-EC has been shown not to be carcinogenic
182 when injected on rat nipples (El-Bayoumy et al.
183 1996). While 5,6-EC is known since a very long
184 time (Schroepfer 2000), it is only recently that
185 their reactivity toward nucleophilic substances
186 including nucleic acid bases was tested. 5,6-EC
187 was shown to be exceptionally stable and totally
188 un-reactive toward nucleophiles including gua-
189 nine, at ambient and physiological temperature,
190 as opposed to the carcinogen styrene-oxide
191 (Paillasse et al. 2012). Importantly, 5,6-EC was
192 stable for several days in the presence of
193 extremely high concentrations of nucleophiles,
194 ruling out that 5,6-EC is spontaneously reactive
195 and behave like direct carcinogenic or alkylating
196 agents. Thus, the unreactivity of 5,6-EC
197 diastereoisomers toward nucleophiles suggests
198 that the biological function of ChEH is not to
199 detoxify cells from 5,6-EC by metabolizing
200 them into a more soluble CT as it was first
201 suggested (Morin et al. 1991).

phytosterol (Aringer and Eneroth 1974). 206
7-dehydrocholesterol-5,6β-epoxide was reported 207
to be an irreversible inhibitor of ChEH (Nashed 208
et al. 1986) (Fig. 8.5). Other steroidal epoxides 209
were not reported to date to be substrates or 210
inhibitors of ChEH. Fatty acid and sulfate esters 211
of cholesterol are not inhibitors of ChEH and thus 212
not substrate of the enzyme showing that esterifi- 213
cation provide against the hydration of chole- 214
sterol-5,6-epoxides by the ChEH (De Medina 215
et al. 2010). Fatty acid and sulfate esters of 216
5,6-EC are not inhibitors of ChEH (Fig. 8.5) 217
(De Medina et al. 2010). Epoxides of PUFA that 218
were reported to be inhibitors of ChEH 219
(De Medina et al. 2010) have not yet being tested 220
as substrates and inhibitors of ChEH. 221

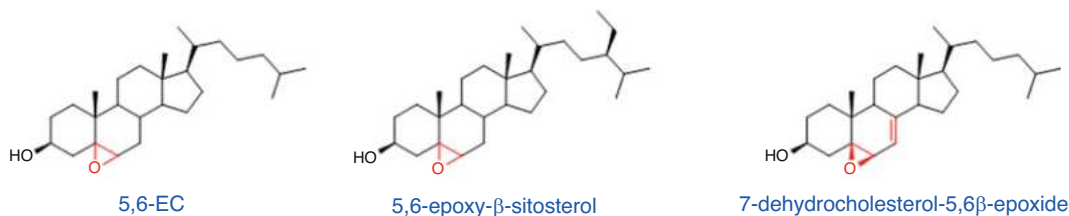
8.5 Subcellular Localization, Tissue Distribution and Regulation of ChEH

8.4 ChEH Substrates

203 ChEH is very specific to the hydrolysis of 5,6-EC
204 into CT. It was shown to hydrolyze
205 5,6-epoxy-β-sitosterol, one of the major

EBP and DHCR7 co-localized in the endoplasmic 225
reticulum of cells (Koczok et al. 2019) were cho- 226
lesterol biosynthesis takes place (Dietschy and 227
Turley 2004). These enzymes are expressed in 228
most mammalian tissues (liver, kidney, lung, 229
testes, spleen, brain, intestinal epithelium, and 230

A



B

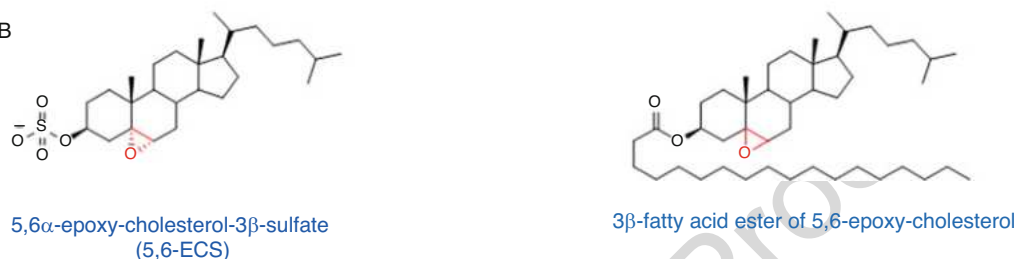


Fig. 8.5 Chemical structure of (a) ChEH substrates and (b) nonsubstrates

skin), with the liver being the richest source (see Human Protein Atlas, <https://www.proteinatlas.org/>). EBP and DHCR7 together with DHCR24 have been shown to colocalize on in the nuclear envelope (Koczok et al. 2019). Consistently, ChEH is mainly present in the microsomes (sub-cellular fractions that contain the reticulum endoplasmic) of various tissues including the liver. ChEH is also found in tumor cells of different tissue origins ((Silvente-Poirot and Poirot 2012) and (M. Poirot and S. Silvente-Poirot, personal communication)). Since EBP and DHCR7 have been reported to be upregulated in several cancers (Kuzu et al. 2016), it is still to be defined what would be the impact of various EBP/DHCR7 ratio on ChEH activity.

8.6 Biological Functions of the ChEH

ChEH enzymatic function is to produce CT and to control 5,6-EC levels. So we must consider the metabolism and the biological properties of CT, 5,6 α -EC and 5,6 β -EC and their metabolites.

8.6.1 Biological Properties of CT and Its Metabolites

CT was reported to be one of the most potent cytotoxic oxysterol (Schroepfer 2000), with little effect on cholesterol biosynthesis downregulation (Morin and Peng 1989). It was reported to inhibit the osteoblastic differentiation and to induce apoptosis suggesting it is a common factor underlying the pathogenesis of atherosclerosis and osteoporosis (Liu et al. 2005). CT was shown to inhibit prostate cancer cell proliferation migration and invasion via a modulation of LXR (Lin et al. 2013). CT has been shown to be a neuroprotective endogenous compound that protects against neuronal injury by direct binding and by inducing a negative modulation on NMDA receptors (Hu et al. 2014). CT suppresses neuronal hyperexcitability through a direct interaction with the voltage-gated sodium channel (Tang et al. 2018). CT was shown to induce vascular smooth cells calcification, which may be a mechanism through which CT favors the formation of the atherosclerotic plaque (Liu et al. 2004, 2007).

On the other side, CT has been shown to be a precursor of secondary metabolites involved in the control of carcinogenic programs. CT is genotoxic through reactive oxygen species production (Cheng et al. 2005) and can be metabolized into oncosterone by the 11- β -hydroxysteroid dehydrogenase of type 2. Oncosterone was shown to be a tumor promoter in breast cancer and is a ligand of GR and LXR (Voisin et al. 2017). Oncosterone is a biased agonist on GR that drives cellular proliferative programs (De Medina et al. 2021; Silvente-Poirot et al. 2018a; Poirot et al. 2018; Voisin et al. 2017).

CT is probably also prone to sulfation by the sulfotransferase SULT2B1b, since B-ring oxysterols are substrates of the enzyme but this deserves further evaluation (Fuda et al. 2007) and should give cholestane-5 α ,6 β -diol-3 β -*O*-sulfate (CDS) which could serve as a modulator of LXR (Song et al. 2001). However, assessment of the biological properties of CDS is difficult because it can be hydrolyzed by the steroid sulfatase (STS) which is widely expressed in human tissues (<https://www.proteinatlas.org/ENSG00000101846-STS/tissue>) to give back CT from CDS. So recently de Medina et al. have developed a non-hydrolyzable analog of CDS to test if CDS could be a biologically active metabolite (de Medina et al., Manuscript submitted for publication). CT is also known as a biomarker of several pathologies (Zanjani et al. 2023; Unluturk et al. 2023; Cooper et al. 2020; Vonica et al. 2019; Reddy et al. 1977) and inherited diseases such as Niemann–Pick C1 disease (Porter et al. 2010).

8.6.2 Biological Properties of 5,6 β -EC and Its Metabolites

5,6 β -EC has not been shown to be a ligand of LXRs and it was reported to display LXR modulatory activities which are cell specific (Segala et al. 2013; Berrodin et al. 2010). 5,6 β -EC is a good substrate for ChEH and a better substrate on whole cell assays (Voisin et al. 2017; De Medina et al. 2010) showing that it may have a major

contribution as a preferred substrate of ChEH for the production of CT and its metabolites such as oncosterone. 5,6 β -EC does not activate the acyl-coA:cholesterol acyl transferase 1 (ACAT1/SOAT1) and is a weak substrate of ACAT1 (Zhang et al. 2003). It is a substrate of the human plasma lecithin-cholesterol acyltransferase (LCAT) (Szedlacsek et al. 1995). 5,6 β -EC was shown to be a weak substrate of SULT2B1b (Fuda et al. 2007). High concentrations in 5,6 β -EC was shown to induce cell death through the impairment of the mitochondrial activity (Segala et al. 2013; Vejux et al. 2007; Lordan et al. 2007; O'Callaghan et al. 2001).

8.6.3 Biological Properties of 5,6 α -EC and Its Metabolites

5,6 α -EC has been shown to be a ligand and modulator of LXRs with cell-specific activities (Segala et al. 2013; Berrodin et al. 2010). 5,6 α -EC is one of the best substrates of the sulfotransferase SULT2B1b (Fuda et al. 2007) to give 5,6 α -epoxy-cholesterol-3 β -sulfate (5,6-ECS). 5,6-ECS was shown to act as the mediator of the breast cancers cells redifferentiation properties of AEBS ligands (Segala et al. 2013) and to be a LXR modulator (Segala et al. 2013; Song et al. 2001). 5,6 α -EC is a potent activator and substrate of the acyl-coA: cholesterol acyl transferase 1 (ACAT1/SOAT1) expressed on the endoplasmic reticulum of cells to produce 5,6 α -EC- and cholesteryl-fatty acid esters (Zhang et al. 2003) while it was reported that plasmatic lecithin-cholesterol-acyl-transferase (LCAT) contributes little for fatty acid esterification of 5,6 α -EC (Yamamuro et al. 2020). Cholesteryl esters display tumor promoter properties (Websdale et al. 2022; Khallouki et al. 2018; Paillasse et al. 2009) but the eventual tumor promoter properties of 5,6 α -EC-fatty acid esters have yet not been investigated and deserve further investigations. More interestingly, 5,6 α -EC is the precursor of dendrogenin A (DDA), dendrogenin B (ddb), C17 compound that were all found as metabolites present in

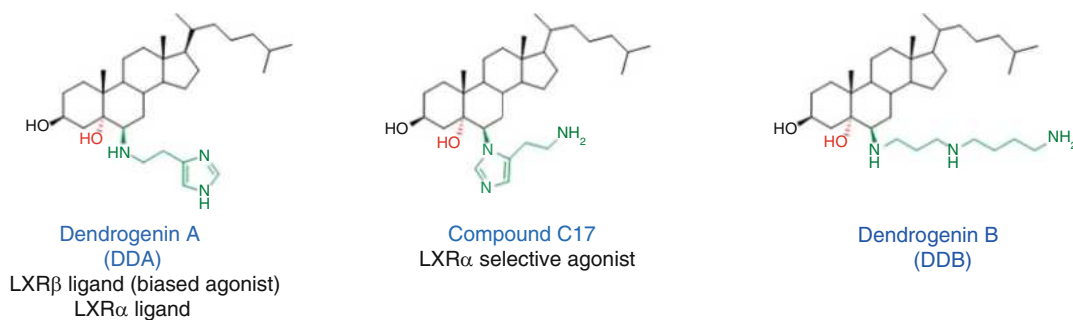


Fig. 8.6 Chemical structure of DDA, C17, and DDB. These compounds are 5,6α-EC natural mammalian metabolites

mammalian tissues (Fig. 8.6) (Soules et al. 2019; De Medina et al. 2013). DDA and C17 are two regioisomers that result from the conjugation of 5,6α-EC with histamine by its primary amine and by its imidazole ring, respectively, and DDB is a 5,6α-EC conjugate with a primary amine of spermidine (Soules et al. 2019; Noguer et al. 2017; De Medina et al. 2009) (Fig. 8.6). DDA is a bioactive conjugated oxysterol that has been proved to be a tumor suppressor metabolite that induces cancer cell redifferentiation, production of antitumor exosomes and at sub micromolar concentrations it induces a lethal autophagy while the DDA regio-isomer C17 was found inactive on these effects (De Medina et al. 2009, 2013, 2021, 2023; Record et al. 2022; Serhan et al. 2020; Mouchel et al. 2020; Bauriaud-Mallet et al. 2019; Silvente-Poirot et al. 2016, 2018b; Poirot and Silvente-Poirot 2016, 2018; Segala et al. 2017; Dalenc et al. 2015; Silvente-Poirot and Poirot 2014). While it was reported that the receptor responsible for its tumor suppressive effects is the LXRβ, it is a ligand of both LXRα and LXRβ (Segala et al. 2017), so it is not yet unknown what could be the biological effects of DDA mediated by LXRα if any. DDA is not an agonist of LXR but a biased agonist. As opposed to canonical LXR ligands, it is a weak antagonist on some LXR-dependent genes such as ABCA1 and an agonist on LDLR expression and on the control of genes involved in cell differentiation, some lipids biosynthesis enzymes, and the control of lysosomes formation and autophagy processes (De Medina et al. 2023; Record et al. 2022;

Serhan et al. 2020; Mouchel et al. 2020; Bauriaud-Mallet et al. 2019; Silvente-Poirot et al. 2018a, b; Poirot and Silvente-Poirot 2018; Segala et al. 2017). DDA is also a very potent inhibitor of the ChEH and of oncosterone formation highlighting the existence of a regulation loop at the ChEH level (De Medina et al. 2021; Poirot et al. 2018; Poirot and Silvente-Poirot 2018; Voisin et al. 2017; De Medina et al. 2013). The C17 compound, which is the inactive regio-isomer of DDA on the induction of cell death and differentiation (Segala et al. 2017; De Medina et al. 2009, 2013) was shown to be, on a LXR-dependent luciferase cell system, a selective LXRα agonist (Segala et al. 2017).

DDB was shown to be a potent inductor of the redifferentiation of glioma and neuroblastoma cell lines into cells with morphological and phenotypical features of glutaminergic neurons (De Medina et al. 2009). A similar effect was observed with DDA but DDA redifferentiation effect was not restricted to these cell lines (Fig. 8.7) (De Medina et al. 2009). DDA and DDB induced the proliferation, sphere formation, and differentiation on adult mice neural stem cell and restore neural responsiveness after injury suggesting that they can contribute to compensate neuronal loss (Fransson et al. 2015; Khalifa et al. 2014).

Together these data showed that dendrogenin A and B constitute a new class of bioactive oxysterols. These conjugates are cationic alkylamino-oxysterols.

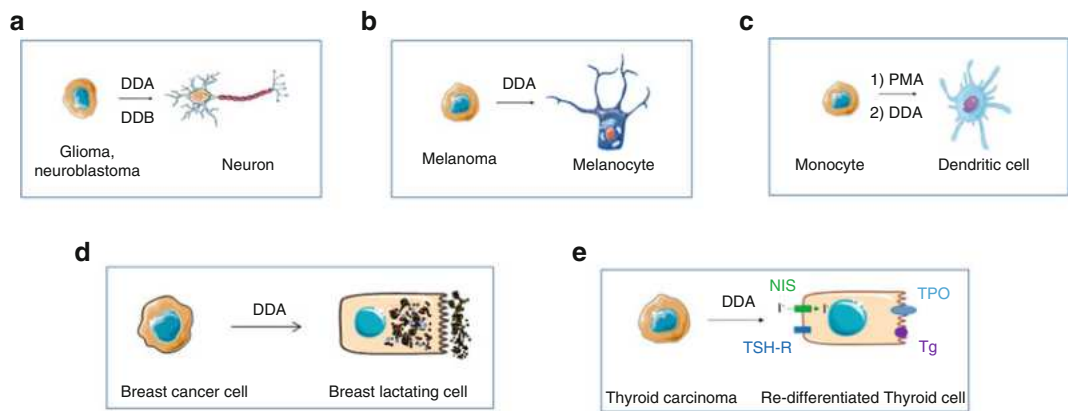


Fig. 8.7 Dendrogenins are bioactive metabolites of 5,6 α -EC. (a) DDA and DDB induce the differentiation of glioma, neuroblastoma, and pluripotent progenitor cells into glutaminergic neurons. (b–e) pluripotency of DDA to differentiate cancer cells. (b) DDA induces the differentiation of melanoma cells into melanocyte, (c) of monocyte

into dendritic cells, (d) of breast cancer cells into lactogenic cells, and (e) of thyroid carcinoma cells into functional thyrocytes. NIS, sodium iodide symporter; TPO, thyroperoxidase; Tg, thyroglobulin; TSH-R, thyroid stimulating hormone receptor

8.7 Regulation of ChEH

Little is known on that topic. We noticed a work from Faye et al. showing that AEBS (also known as ABS at that time) from rat uterus increased during estrus (Faye et al. 1980) suggesting that female sex steroid hormones could regulate ChEH activity. This is supported by more recent data showing that the overexpression of ER α increased cholesterologenesis through the upregulation of gene encoding cholesterologenesis enzymes under the transcriptional control of SREBP2 in mice (Wang et al. 2006). In addition, it is reported that both EBP (Misawa et al. 2003) and DHCR7 (Prabhu et al. 2014) are under the transcriptional control of SREBP2. Together these data suggest that the ChEH activity can be modulated by female sex steroid hormones. The fact that DHCR7 can be regulated by AMP kinase and protein kinase A (Prabhu et al. 2017) suggests that ChEH activity could be controlled by cell surface signaling (Patel and Smith 2023; London and Stratakis 2022) and nutrient sensing (Gonzalez et al. 2020).

8.8 Conclusion

We report on this chapter our current knowledge on the ChEH enzyme and propose future research directions. We show that ChEH constitutes a metabolic checkpoint controlling the production of bioactive metabolites such as dendrogenins, CT, oncosterone and probably other yet unknown metabolites. This illustrates the existence of a new fascinating metabolic branch on the cholesterol pathway. This new branch deserves further investigations that will led to a better understanding of fine processes involved on mammalian development, physiology and that may give new clues to improve our understanding of several degenerative diseases and aging processes.

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References

- Aringer L, Eneroth P (1974) Formation and metabolism in vitro of 5,6-epoxides of cholesterol and beta-sitosterol. *J Lipid Res* 15:389–398
- Bauriaud-Mallet M, Vija-Racaru L, Brillouet S, Mallinger A, De Medina P, Rives A, Payre B, Poirot M, Courbon F, Silvente-Poirot S (2019) The cholesterol-derived metabolite dendrogenin A functionally reprograms breast adenocarcinoma and undifferentiated thyroid cancer cells. *J Steroid Biochem Mol Biol* 192:105390
- Berrodin TJ, Shen Q, Quinet EM, Yudit MR, Freedman LP, Nagpal S (2010) Identification of 5alpha, 6alpha-epoxycholesterol as a novel modulator of liver X receptor activity. *Mol Pharmacol* 78:1046–1058
- Black HS, Lo WB (1971) Formation of a carcinogen in human skin irradiated with ultraviolet light. *Nature* 234:306–308
- Caprariello AV, Adams DJ (2022) The landscape of targets and lead molecules for remyelination. *Nat Chem Biol* 18:925–933
- Chan JT, Black HS (1974) Skin carcinogenesis: cholesterol-5alpha,6alpha-epoxide hydase activity in mouse skin irradiated with ultraviolet light. *Science* 186:1216–1217
- Cheng YW, Kang JJ, Shih YL, Lo YL, Wang CF (2005) Cholesterol-3-beta, 5-alpha, 6-beta-triol induced genotoxicity through reactive oxygen species formation. *Food Chem Toxicol* 43:617–622
- Cooper JA, Church HJ, Wu HY (2020) Cholestane-3beta, 5alpha, 6beta-triol: Further insights into the performance of this oxysterol in diagnosis of Niemann-Pick disease type C. *Mol Genet Metab* 130:77–86
- Dalenc F, Poirot M, Silvente-Poirot S (2015) Dendrogenin A: a mammalian metabolite of cholesterol with tumor suppressor and neurostimulating properties. *Curr Med Chem* 22:3533–3549
- De Medina P, Paillasse MR, Payre B, Silvente-Poirot S, Poirot M (2009) Synthesis of new alkylaminoxyterols with potent cell differentiating activities: identification of leads for the treatment of cancer and neurodegenerative diseases. *J Med Chem* 52:7765–7777
- De Medina P, Paillasse MR, Segala G, Poirot M, Silvente-Poirot S (2010) Identification and pharmacological characterization of cholesterol-5,6-epoxide hydrolase as a target for tamoxifen and AEBs ligands. *Proc Natl Acad Sci U S A* 107:13520–13525
- De Medina P, Paillasse MR, Segala G, Voisin M, Mhamdi L, Dalenc F, Lacroix-Triki M, Filleron T, Pont F, Saati TA, Morisseau C, Hammock BD, Silvente-Poirot S, Poirot M (2013) Dendrogenin A arises from cholesterol and histamine metabolism and shows cell differentiation and anti-tumour properties. *Nat Commun* 4:1840
- De Medina P, Diallo K, Huc-Claustre E, Attia M, Soules R, Silvente-Poirot S, Poirot M (2021) The 5,6-epoxycholesterol metabolic pathway in breast cancer: Emergence of new pharmacological targets. *Br J Pharmacol* 178:3248–3260
- De Medina P, Bunay J, Poirot M, Record M, Silvente-Poirot S (2023) Targeting NR1H/liver X receptor with dendrogenin A differentiates tumor cells to activate a new secretory pathway releasing immunogenic anti-tumor vesicles enriched in LC3-II-associated exosomes. *Autophagy* 19:1036–1038
- Dietschy JM, Turley SD (2004) Thematic review series: brain lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animal. *J Lipid Res* 45:1375–1397
- El-Bayoumy K, Ji BY, Upadhyaya P, Chae YH, Kurtzke C, Rivenson A, Reddy BS, Amin S, Hecht SS (1996) Lack of tumorigenicity of cholesterol epoxides and estrone-3,4-quinone in the rat mammary gland. *Cancer Res* 56:1970–1973
- Faye JC, Lasserre B, Bayard F (1980) Antiestrogen specific, high affinity saturable binding sites in rat uterine cytosol. *Biochem Biophys Res Commun* 93:1225–1231
- Fransson A, De Medina P, Paillasse MR, Silvente-Poirot S, Poirot M, Ulfendahl M (2015) Dendrogenin A and B two new steroidal alkaloids increasing neural responsiveness in the deafened guinea pig. *Front Aging Neurosci* 7:145
- Fuda H, Javitt NB, Mitamura K, Ikegawa S, Strott CA (2007) Oxysterols are substrates for cholesterol sulfotransferase. *J Lipid Res* 48:1343–1352
- Gonzalez A, Hall MN, Lin SC, Hardie DG (2020) AMPK and TOR: The Yin and Yang of cellular nutrient sensing and growth control. *Cell Metab* 31:472–492
- Han F, Zhou MM (2019) Small molecules with big promises for curing demyelinating diseases. *Cell Chem Biol* 26:468–470
- Hu H, Zhou Y, Leng T, Liu A, Wang Y, You X, Chen J, Tang L, Chen W, Qiu P, Yin W, Huang Y, Zhang J, Wang L, Sang H, Yan G (2014) The major cholesterol metabolite cholestane-3beta,5alpha,6beta-triol functions as an endogenous neuroprotectant. *J Neurosci* 34:11426–11438
- Hubler Z, Allimuthu D, Bederman I, Elitt MS, Madhavan M, Allan KC, Shick HE, Garrison E, Karl MT, Factor DC, Nevin ZS, Sax JL, Thompson MA, Fedorov Y, Jin J, Wilson WK, Giera M, Bracher F, Miller RH, Tesar PJ, Adams DJ (2018) Accumulation of 8,9-unsaturated sterols drives oligodendrocyte formation and remyelination. *Nature* 560:372–376
- Kedjourn B, De Medina P, Oulad-Abdelghani M, Payre B, Silvente-Poirot S, Favre G, Faye JC, Poirot M (2004) Molecular characterization of the microsomal tamoxifen binding site. *J Biol Chem* 279:34048–34061
- Khalifa SA, De Medina P, Erlandsson A, El-Seedi HR, Silvente-Poirot S, Poirot M (2014) The novel steroidal alkaloids dendrogenin A and B promote proliferation of adult neural stem cells. *Biochem Biophys Res Commun* 446:681–686
- Khalouki F, Owen RW, Silvente-Poirot S, Poirot M (2018) Bryonolic acid blocks cancer cell clonogenicity

- and invasiveness through the inhibition of fatty acid: cholesteryl ester formation. *Biomedicines* 6(1):21
- Koczk K, Gurumurthy CB, Balogh I, Korade Z, Mirnics K (2019) Subcellular localization of sterol biosynthesis enzymes. *J Mol Histol* 50:63–73
- Kuzu OF, Noory MA, Robertson GP (2016) The role of cholesterol in cancer. *Cancer Res* 76:2063–2070
- Leignadier J, Dalenc F, Poirot M, Silvente-Poirot S (2017) Improving the efficacy of hormone therapy in breast cancer: The role of cholesterol metabolism in SERM-mediated autophagy, cell differentiation and death. *Biochem Pharmacol* 144:18–28
- Lin CY, Huo C, Kuo LK, Hiipakka RA, Jones RB, Lin HP, Hung Y, Su LC, Tseng JC, Kuo YY, Wang YL, Fukui Y, Kao YH, Kokontis JM, Yeh CC, Chen L, Yang SD, Fu HH, Chen YW, Tsai KK, Chang JY, Chu CP (2013) Cholestane-3 β , 5 α , 6 β -triol suppresses proliferation, migration, and invasion of human prostate cancer cells. *PLoS One* 8:e65734
- Liu H, Yuan L, Xu S, Zhang T, Wang K (2004) Cholestane-3 β , 5 α , 6 β -triol promotes vascular smooth muscle cells calcification. *Life Sci* 76:533–543
- Liu H, Yuan L, Xu S, Wang K, Zhang T (2005) Cholestane-3 β , 5 α , 6 β -triol inhibits osteoblastic differentiation and promotes apoptosis of rat bone marrow stromal cells. *J Cell Biochem* 96:198–208
- Liu H, Yuan L, Xu S, Wang K (2007) Endothelial cell and macrophage regulation of vascular smooth muscle cell calcification modulated by cholestane-3 β , 5 α , 6 β -triol. *Cell Biol Int* 31:900–907
- Lo W, Black HS (1973) Inhibition of carcinogen formation in skin irradiated with ultraviolet light. *Nature* 246:489–491
- London E, Stratakis CA (2022) The regulation of PKA signaling in obesity and in the maintenance of metabolic health. *Pharmacol Ther* 237:108113
- Long T, Hassan A, Thompson BM, McDonald JG, Wang J, Li X (2019) Structural basis for human sterol isomerase in cholesterol biosynthesis and multidrug recognition. *Nat Commun* 10:2452
- Lordan S, O'Callaghan YC, O'Brien NM (2007) Death-signaling pathways in human myeloid cells by oxLDL and its cytotoxic components 7 β -hydroxycholesterol and cholesterol-5 β , 6 β -epoxide. *J Biochem Mol Toxicol* 21:362–372
- Misawa K, Horiba T, Arimura N, Hirano Y, Inoue J, Emoto N, Shimano H, Shimizu M, Sato R (2003) Sterol regulatory element-binding protein-2 interacts with hepatocyte nuclear factor-4 to enhance sterol isomerase gene expression in hepatocytes. *J Biol Chem* 278:36176–36182
- Morin RJ, Peng SK (1989) The role of cholesterol oxidation products in the pathogenesis of atherosclerosis. *Ann Clin Lab Sci* 19:225–237
- Morin RJ, Hu B, Peng SK, Sevanian A (1991) Cholesterol oxides and carcinogenesis. *J Clin Lab Anal* 5:219–225
- Morisseau C (2013) Role of epoxide hydrolases in lipid metabolism. *Biochimie* 95:91–95
- Mouchel PL, Serhan N, Betous R, Farge T, Saland E, De Medina P, Hoffmann JS, Sarry JE, Poirot M, Silvente-Poirot S, Recher C (2020) Dendrogenin A enhances anti-leukemic effect of anthracycline in acute myeloid leukemia. *Cancers (Basel)* 12(10):2933
- Nashed NT, Michaud DP, Levin W, Jerina DM (1985) Properties of liver microsomal cholesterol 5,6-oxide hydrolase. *Arch Biochem Biophys* 241:149–162
- Nashed NT, Michaud DP, Levin W, Jerina DM (1986) 7-Dehydrocholesterol 5,6 β -oxide as a mechanism-based inhibitor of microsomal cholesterol oxide hydrolase. *J Biol Chem* 261:2510–2513
- Newman JW, Morisseau C, Hammock BD (2005) Epoxide hydrolases: their roles and interactions with lipid metabolism. *Prog Lipid Res* 44:1–51
- Noguer E, Soules R, Netter C, Nagarathinam C, Leignadier J, Huc-Claustre E, Serhan N, Rives A, De Medina P, Silvente-Poirot S, Poirot M (2017) Quantitative analysis of the tumor suppressor dendrogenin A using liquid chromatography tandem mass spectrometry. *Chem Phys Lipids* 207:81–86
- O'Callaghan YC, Woods JA, O'Brien NM (2001) Comparative study of the cytotoxicity and apoptosis-inducing potential of commonly occurring oxysterols. *Cell Biol Toxicol* 17:127–137
- Paillasse MR, De Medina P, Amouroux G, Mhamdi L, Poirot M, Silvente-Poirot S (2009) Signaling through cholesterol esterification: a new pathway for the cholecystokinin 2 receptor involved in cell growth and invasion. *J Lipid Res* 50:2203–2211
- Paillasse MR, Saffon N, Gornitzka H, Silvente-Poirot S, Poirot M, De Medina P (2012) Surprising unreactivity of cholesterol-5,6-epoxides towards nucleophiles. *J Lipid Res* 53:718–725
- Patel K, Smith NJ (2023) Primary cilia, A-kinase anchoring proteins and constitutive activity at the orphan G protein-coupled receptor GPR161: A tale about a tail. *Br J Pharmacol*. <https://doi.org/10.1111/bph.16053>
- Poirot M, Silvente-Poirot S (2013) Cholesterol-5,6-epoxides: chemistry, biochemistry, metabolic fate and cancer. *Biochimie* 95:622–631
- Poirot M, Silvente-Poirot S (2016) When cholesterol meets histamine, it gives rise to dendrogenin A: a tumour suppressor metabolite. *Biochem Soc Trans* 44:631–637
- Poirot M, Silvente-Poirot S (2018) The tumor-suppressor cholesterol metabolite, dendrogenin A, is a new class of LXR modulator activating lethal autophagy in cancers. *Biochem Pharmacol* 153:75–81
- Poirot M, Soules R, Mallinger A, Dalenc F, Silvente-Poirot S (2018) Chemistry, biochemistry, metabolic fate and mechanism of action of 6-oxo-cholestan-3 β , 5 α -diol (OCDO), a tumor promoter and cholesterol metabolite. *Biochimie* 153:139–149
- Porter FD, Scherrer DE, Lanier MH, Langmade SJ, Molugu V, Gale SE, Olzeski D, Sidhu R, Dietzen DJ, Fu R, Wassif CA, Yanjanin NM, Marso SP, House J, Vite C, Schaffer JE, Ory DS (2010) Cholesterol oxidation products are sensitive and specific blood-based

- biomarkers for Niemann-Pick C1 disease. *Sci Transl Med* 2:56ra81
- Prabhu AV, Sharpe LJ, Brown AJ (2014) The sterol-based transcriptional control of human 7-dehydrocholesterol reductase (DHCR7): Evidence of a cooperative regulatory program in cholesterol synthesis. *Biochim Biophys Acta* 1842:1431–1439
- Prabhu AV, Luu W, Sharpe LJ, Brown AJ (2017) Phosphorylation regulates activity of 7-dehydrocholesterol reductase (DHCR7), a terminal enzyme of cholesterol synthesis. *J Steroid Biochem Mol Biol* 165:363–368
- Record M, Attia M, Carayon K, Pucheu L, Bunay J, Soules R, Ayadi S, Payre B, Perrin-Cocon L, Bourgaill F, Lamaziere A, Lotteau V, Poirot M, Silvente-Poirot S, Medina DE, P. (2022) Targeting the liver X receptor with dendrogenin A differentiates tumour cells to secrete immunogenic exosome-enriched vesicles. *J Extracell Vesicles* 11:e12211
- Reddy BS, Martin CW, Wynder EL (1977) Fecal bile acids and cholesterol metabolites of patients with ulcerative colitis, a high-risk group for development of colon cancer. *Cancer Res* 37:1697–1701
- Sax JL, Hershman SN, Hubler Z, Allimuthu D, Eliot MS, Bederman I, Adams DJ (2022) Enhancers of human and rodent oligodendrocyte formation predominantly induce cholesterol precursor accumulation. *ACS Chem Biol* 17:2188–2200
- Schroepfer GJ Jr (2000) Oxysterols: modulators of cholesterol metabolism and other processes. *Physiol Rev* 80: 361–554
- Segala G, De Medina P, Iuliano L, Zerbinati C, Paillasse MR, Noguier E, Dalenc F, Payre B, Jordan VC, Record M, Silvente-Poirot S, Poirot M (2013) 5,6-Epoxy-cholesterols contribute to the anticancer pharmacology of tamoxifen in breast cancer cells. *Biochem Pharmacol* 86:175–189
- Segala G, David M, De Medina P, Poirot MC, Serhan N, Vergez F, Mougél A, Saland E, Carayon K, Leignadier J, Caron N, Voisin M, Cherier J, Ligat L, Lopez F, Noguier E, Rives A, Payre B, Saati TA, Lamaziere A, Despres G, Lobaccaro JM, Baron S, Demur C, De Toni F, Larrue C, Boutzen H, Thomas F, Sarry JE, Tosolini M, Picard D, Record M, Recher C, Poirot M, Silvente-Poirot S (2017) Dendrogenin A drives LXR to trigger lethal autophagy in cancers. *Nat Commun* 8:1903
- Serhan N, Mouchel PL, Medina P, Segala G, Mougél A, Saland E, Rives A, Lamaziere A, Despres G, Sarry JE, Larrue C, Vergez F, Largeaud L, Record M, Recher C, Silvente-Poirot S, Poirot M (2020) Dendrogenin A synergizes with cytarabine to kill acute myeloid leukemia cells in vitro and in vivo. *Cancers (Basel)* 12(7): 1725
- Sevanian A, Mcleod LL (1986) Catalytic properties and inhibition of hepatic cholesterol-epoxide hydrolase. *J Biol Chem* 261:54–59
- Silvente-Poirot S, Poirot M (2012) Cholesterol epoxide hydrolase and cancer. *Curr Opin Pharmacol* 12:696–703
- Silvente-Poirot S, Poirot M (2014) Cancer. Cholesterol and cancer, in the balance. *Science* 343:1445–1446
- Silvente-Poirot S, De Medina P, Record M, Poirot M (2016) From tamoxifen to dendrogenin A: The discovery of a mammalian tumor suppressor and cholesterol metabolite. *Biochimie* 130:109–114
- Silvente-Poirot S, Dalenc F, Poirot M (2018a) The effects of cholesterol-derived oncometabolites on nuclear receptor function in cancer. *Cancer Res* 78:4803–4808
- Silvente-Poirot S, Segala G, Poirot MC, Poirot M (2018b) Ligand-dependent transcriptional induction of lethal autophagy: A new perspective for cancer treatment. *Autophagy* 14:555–557
- Song C, Hiipakka RA, Liao S (2001) Auto-oxidized cholesterol sulfates are antagonistic ligands of liver X receptors: implications for the development and treatment of atherosclerosis. *Steroids* 66:473–479
- Soules R, Audouard-Combe F, Huc-Claustre E, De Medina P, Rives A, Chatelut E, Dalenc F, Franchet C, Silvente-Poirot S, Poirot M, Allal B (2019) A fast UPLC-HILIC method for an accurate quantification of dendrogenin A in human tissues. *J Steroid Biochem Mol Biol* 194:105447
- Szedlacsek SE, Wasowicz E, Hulea SA, Nishida HI, Kummerow FA, Nishida T (1995) Esterification of oxysterols by human plasma lecithin-cholesterol acyltransferase. *J Biol Chem* 270:11812–11819
- Tang L, Yan M, Leng T, Yin W, Cai S, Duan S, Zhu W, Lin S, Huang J, Yan G, Zheng G, Chen Y (2018) Cholestane-3 β , 5 α , 6 β -triol suppresses neuronal hyperexcitability via binding to voltage-gated sodium channels. *Biochem Biophys Res Commun* 496:95–100
- Theodoropoulos PC, Wang W, Budhipramono A, Thompson BM, Madhusudhan N, Mitsche MA, McDonald JG, De Brabander JK, Nijhawan D (2020) A medicinal chemistry-driven approach identified the sterol isomerase EBP as the molecular target of TASIN colorectal cancer toxins. *J Am Chem Soc* 142:6128–6138
- Unluturk U, Bahcecioğlu AB, Samadi A, Lay I, Bayraktar M, Dagdelen S (2023) Glycemic variability leads to higher levels of auto-oxidized oxysterol species in patients with type 1 diabetes mellitus. *J Endocrinol Invest.* <https://doi.org/10.1007/s40618-023-02110-7>
- Vejux A, Kahn E, Menetrier F, Montange T, Lherminier J, Riedinger JM, Lizard G (2007) Cytotoxic oxysterols induce caspase-independent myelin figure formation and caspase-dependent polar lipid accumulation. *Histochem Cell Biol* 127:609–624
- Voisin M, De Medina P, Mallinger A, Dalenc F, Huc-Claustre E, Leignadier J, Serhan N, Soules R, Segala G, Mougél A, Noguier E, Mhamdi L, Bacquie E, Iuliano L, Zerbinati C, Lacroix-Triki M, Chaltiel L, Filleron T, Cavailles V, Al Saati T, Rochaix P, Duprez-Paumier R, Franchet C, Ligat L, Lopez F, Record M, Poirot M, Silvente-Poirot S (2017) Identification of a tumor-promoter cholesterol

- metabolite in human breast cancers acting through the glucocorticoid receptor. *Proc Natl Acad Sci U S A* 114: E9346–E9355
- Vonica CL, Ilie IR, Socaciu C, Moraru C, Georgescu B, Farcas A, Roman G, Muresan AA, Georgescu CE (2019) Lipidomics biomarkers in women with polycystic ovary syndrome (PCOS) using ultra-high performance liquid chromatography-quadrupole time of flight electrospray in a positive ionization mode mass spectrometry. *Scand J Clin Lab Invest* 79:437–442
- Wang HH, Afdhal NH, Wang DQ (2006) Overexpression of estrogen receptor alpha increases hepatic cholesterogenesis, leading to biliary hypersecretion in mice. *J Lipid Res* 47:778–786
- Wang W, Zhang L, Morlock L, Williams NS, Shay JW, De Brabander JK (2019) Design and synthesis of TASIN analogues specifically targeting colorectal cancer cell lines with mutant adenomatous polyposis coli (APC). *J Med Chem* 62:5217–5241
- Watabe T, Sawahata T (1979) Biotransformation of cholesterol to cholestane-3beta,5alpha,6beta-triol via cholesterol alpha-epoxide (5alpha,6alpha-epoxycholestan-3beta-ol) in bovine adrenal cortex. *J Biol Chem* 254: 3854–3860
- Websdale A, Kiew Y, Chalmers P, Chen X, Cioccoloni G, Hughes TA, Luo X, Mwarzi R, Poirot M, Roberg-Larsen H, Wu R, Xu M, Zulyniak MA, Thorne JL (2022) Pharmacologic and genetic inhibition of cholesterol esterification enzymes reduces tumour burden: A systematic review and meta-analysis of preclinical models. *Biochem Pharmacol* 196:114731
- Yamamuro D, Yamazaki H, Osuga JI, Okada K, Wakabayashi T, Takei A, Takei S, Takahashi M, Nagashima S, Holleboom AG, Kuroda M, Bujo H, Ishibashi S (2020) Esterification of 4beta-hydroxycholesterol and other oxysterols in human plasma occurs independently of LCAT. *J Lipid Res* 61:1287–1299
- Zanjani BN, Samadi A, Isikhan SY, Lay I, Beyaz S, Gelincik A, Buyukozturk S, Arda N (2023) Plasma levels of oxysterols 7-ketocholesterol and cholestane-3beta, 5alpha, 6beta-triol in patients with allergic asthma. *J Asthma* 60:288–297
- Zhang Y, Yu C, Liu J, Spencer TA, Chang CC, Chang TY (2003) Cholesterol is superior to 7-ketocholesterol or 7 alpha-hydroxycholesterol as an allosteric activator for acyl-coenzyme A:cholesterol acyltransferase 1. *J Biol Chem* 278:11642–11647
- Zhang L, Theodoropoulos PC, Eskiocak U, Wang W, Moon YA, Posner B, Williams NS, Wright WE, Kim SB, Nijhawan D, De Brabander JK, Shay JW (2016) Selective targeting of mutant adenomatous polyposis coli (APC) in colorectal cancer. *Sci Transl Med* 8: 361ra140
- Zhang L, Kim SB, Luitel K, Shay JW (2018) Cholesterol depletion by TASIN-1 induces apoptotic cell death through the ER stress/ROS/JNK signaling in colon cancer cells. *Mol Cancer Ther* 17:943–951
- Zielinski ZAM, Pratt DA (2019) H-atom abstraction vs addition: accounting for the diverse product distribution in the autoxidation of cholesterol and its esters. *J Am Chem Soc* 141:3037–3051